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Exploring the Diverse Roles of Exosomes: Implications in Health and Disease

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Abstract: In the intracellular communication and accurate function of immune cells, the healthy cells release the exosome. Exosomes are natural carrier of DNA, RNA and proteins and very much essential normal physiological system, however in diseased conditions these exosomes may act as a activator of cellular damage and cellular stress. In cancer, exosomes contribute to angiogenesis, invasiveness, and immune evasion, acting as carriers of molecular constituents. Infectious diseases, particularly viral infections, result in the release of exosomes with unique cargoes, serving as potential indicators of infection. In the central nervous system (CNS) diseases, exosome cargoes act as biomarkers, influencing pathogenesis and facilitating disease transmission. Exosomes play significant roles in ischemic stroke, neurodegenerative diseases (such as Alzheimer's and Huntington's), and prion diseases. In Cardiac diseases, exosomes are involved in myocardial repair and endothelial cells communication. The dysregulation of exosome biogenesis contributes to vascular smooth muscle cell calcification. In this review, we rigorously examine the diverse roles of exosomes in pathological processes across various diseases. This thorough analysis is crucial for enhancing our understanding of advancing diagnostics, therapeutics, and overall comprehension of intercellular communication of exosome in both healthy and diseased conditions.

Keywords- Alzheimer's, Atherosclerosis, Huntington's, Prion diseases, Stroke.

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BACKGROUND

An extracellular vesicle (EV) is a lipid bilayer structure secreted by healthy cells in a physiological environment, enriched with proteins and nucleic acids and act as natural carriers. The exosomes transport the nucleic acids, lipids and proteins in cell to adjacent cells (autocrine), cells to nearly located cells (paracrine) and cells to distinctly located cells (endocrine) manner. Generally, these EVs are separated into three classes according to shape, size and diameter. I) Exosomes, which are membrane vesicles derived from multi vesicular bodies and have a diameter of less than 100 nm. II). Micro vesicles, with a size below 1000 nm, formed through the budding of the plasma membrane. III) Apoptotic bodies, exceeding 1000 nm in diameter, are generated through blebbing of the apoptotic cell membrane (Buzas et al., 2023). Exosomes, small extracellular vesicles measuring approximately size 30-120 nm originate from healthy cells at both physiological and disease conditions and commonly found in various biological fluids like semen, breast milk and urine. The endosome maturation, inside budding of multi vesicular bod y are the common methods for synthesis of exosomes. (Doyle et al.,

2019). These exosomes mediate cell-to-cell communication and transfer molecular constituents as like proteins, lipids, heat shock proteins, membrane trafficking proteins and tetraspanins, enzymes to recipient cells and influencing both pathological and physiological processes (Liu et al., 2019, Aheget et al., 2020 and Kalluri et al.,2020).

Exosome Biogenesis

The process of exosome formations starts with the budding of the plasma membrane, which results in the production of early endosomes. Following partial invagination, these endosomes create intraluminal vesicles (ILVs) inside their membranes. These ILVs are further invaginate multiple times and form late endosome and further make multi vascular bodies (MVBs). MVBs are then sent to the trans-Golgi network so that endosome recycling can occur. They have two possible paths: either they can fuse with lysosome for degradation of its content, or it can fuse with plasma membrane for release their content to extra cellular space by exosomes (Yue et al., 2020).

Exosomes in Cancer

In the context of proliferative cancer, several crucial processes occur, including angiogenesis leading to the expansion of cancerous tissue, the acquisition of migratory and invasive capabilities, the development of mechanisms to evade attacks from the immune system, and ultimately, the initiation of metastasis (Gonzalez et al., 2018). Glioblastoma-secreted exosomes promote angiogenesis in vascular endothelial cells (Monteforte et al., 2017). Exosomes from colon cancer carry cell cycle-related mRNA, promoting the proliferation of vascular endothelial cells (Umwali et al.,2021). Renal cancer cells release CD105-positive exosomes, promoting growth in vascular endothelial cells (Gai et al., 2019). Cancer cell exosomes carrying the HSP90 α receptor enhance invasiveness through autocrine mechanisms, activate plasminogen, and increase the degradation of extracellular matrix and E-cadherin (Sager et al., 2022). Colon cancer-derived exosomes express Fas ligand, inducing apoptosis in T cells (Abusamra et al., 2005). Breast cancer cell-derived exosomes contribute to tumor growth by inhibiting the proliferation and activation of NK cells (Abusamra et al., 2005).

Exosomes in Infectious Diseases

In the context of viral infection, cells infected with a virus release exosome more frequently than non-infected cells, serving as potential indicators of viral infection (Saad et al., 2021). For instance, during HIV infection, platelets release an excessive number of exosomes containing mitochondria, differing from those released by normal healthy cells. Exosomes play a crucial role in conveying various cargoes to recipient cells during HIV infection. HIV-infected cells release exosomes containing the Nef (Negative Regulatory Factor) protein, which binds to recipient cells, rendering them susceptible to HIV infection. Additionally, Nef effectively inhibits the release of CD4+ exosomes from T cells, suppressing the viral recognition by immune cells (Rezaie et al., 2021).

Exosomes in Central Nervous System Diseases

Central nervous system (CNS) disorders area rise from ischemic, haemorrhagic, neurodegenerative, inflammatory, and developmental causes. Emerging evidence suggests that the cargos within exosomes play a crucial role in the pathogenesis of CNS diseases, with exosome content serving as biomarkers for specific conditions within the central nervous system (Zhang et al., 2021). Moreover, studies indicate that exosomes primarily contribute to RNA-related signal transduction during different stages of stroke, reflecting the diversity and nature of exosomes cargos (Narang et al., 2022). In ischemic stroke, the exosome release caspase-1 inflammatory protein into circulation and plays major role in brain damage repairing. This caspase-1 can act as potential biomarker for ischemic stroke (Jiang et al., 2022). In ischemia, the cells of CNS like neurons, oligodendrocytes and astrocytes secretes exosomes loaded with microRNA-124 promote neurogenesis (Zhou et al., 2022). Exosomal proteins including mHTT (mutant huntingtin) and miRNAs can be biomarkers and are involved in the pathophysiology of Huntington's disease (HD). These proteins are found in exosomes that are discharged into circulation, making them useful non-invasive peripheral biomarkers that can be used to predict and diagnose a variety of neurodegenerative illnesses (Ananbeh et al., 2021). The exosome loaded with LAMP-1 (Lysosomal-associated membrane protein 1) protein and tau protein in plasma or CSF fluid of Alzheimer's disease (AD) patients may be useful as biomarkers for the early identification of AD (Kim et al., 2021). Further in AD the REST (repressor element 1-silencing transcription factor), HSF-1 (heat-shock factor 1) and IRS (phosphorylated type 1 insulin receptor substrate) are Proteins associated with neurogenic exosomes experience alterations in the plasma of individuals with Alzheimer's disease (AD) up

to a decade before receiving an official diagnosis (Goetzl et al., 2015). Exosomes show a high expression of normal prion protein (PrP^{C}) in prion disorders, which are defined by the misfolding of the prion protein (PrP^{Sc}) resulting in spongiform vacuolation and progressive neuronal death. Furthermore, the presence of the disease-associated form of PrP^{C} in exosomes raises the possibility that it plays a role in the spread of prion disorders between different tissues and the advancement of disease. Furthermore, sphingomyelin, cholesterol, and sphingomyelin GPI-anchored proteins are prevalent in exosomes, suggesting their possible role in protein sorting within exosomes and assisting in the creation of PrP^{Sc} (Prasad et al., 2019).

Exosomes in Cardiac Diseases

Exosomes are extracellular messengers in relation to ischemia signalling and cardiac healing pathways. Several studies have demonstrated that cardiac tissue releases exosomes that contribute to increased cellular communication in the adult heart (Røsand et al., 2021). Cardiomyocytes isolated from myocardial infarction (MI) patients' left ventricles release 50 nm-long, double-membrane-bound exosome-like entities that are encased in multivesicular bodies in the cytoplasm. (Emanueli et al., 2015).

Atherosclerosis, a chronic inflammatory process characterized by the accumulation of lipids and plaque formation on arterial walls, involves endothelial dysfunction as a primary factor. Endothelial dysfunction activates adhesion molecules, recruiting leukocytes, particularly monocytes. Exosomes are believed to mediate communication between endothelial cells, macrophages, and vascular smooth muscle cells in atherosclerosis (Botts et al., 2021). Endothelial cell injury, vascular smooth muscle cells (VSMCs) over express kruppel-like factor-5, leading to an increase in miRNA-155 expression and potentially upregulating the secretion of exosomes containing miRNA-155. Consequently, endothelial integrity is weakened, which raises the risk of atherosclerosis and plaque development (Zheng et al., 2017). Vascular smooth muscle cells (VSMCs) produce exosomes that are rich in miRNA and proteins that control migration and adhesion of cells as well as autocrine and paracrine signalling that affects migration and proliferation. The over expression of calcification and other pathological processes results from an imbalance in the regulation of calcification activators and inhibitors. This process involves the generation of exosomes, which are aided by Sphingomyelin phosphodiesterase 3 (SMPD3). It has been shown that SMPD3 decrease inhibits exocytosis and VSMC calcification (Kapustin et al., 2016).

CONCLUSION

We found that exosomes functions in a variety of diseases, including cancer, illnesses of the neurological system, infectious diseases, and cardiovascular ailments. An important part of the pathophysiology of many illnesses is exosome secretion. Exosomes have been shown to have significant biomedical utility; this is especially true of their ability to serve as biomarkers for early diagnosis.

CONFLICTS OF INTEREST:

None

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